Remarks

Upon entry of the amendments submitted herein, claims 23-82 will be pending. Claims 1-22 have been canceled previously or herein without prejudice or disclaimer. Applicants reserve the right to pursue subject matter encompassed by all canceled claims in one or more continuation or divisional applications. No new matter has been added.

Rejection of claims 23-36, 40-53, 57-66, and 70-79 under 35 U.S.C. § 101

The rejection of claims 23-36, 40-53, 57-66, and 70-79 under 35 U.S.C. § 101 as allegedly not being supported by either a specific and substantial utility or a well established utility was maintained. *See* Paper No. 42005, page 2. In particular, the Examiner maintained the allegation that "the specification fails to provide sufficient objective evidence of any activity for encoded protein" and that "there is no information pertaining to the significance of the percentage homology, e.g. whether there were any conserved motifs that would lead the artisan to accept the protein's function." *See Id.* at 3.

Applicants respectfully disagree and traverse.

In the first Office Action mailed April 21, 2005, the Examiner introduced the currently pending utility rejection alleging that "the specification fails to provide sufficient objective evidence of any activity for encoded protein." *See* Paper No. 92004, page 3, last paragraph. In Applicants response to the first office action, passages from the specification were explicitly identified where an activity for the FcR-V polypeptides was indeed asserted. Specifically, Applicant's response pointed out that the specification indicates that FcR-V polypeptides are "important in the regulation of the immune and hematopoietic systems and are 'thought to function as an important trigger of complex immune defense responses'" and "are thought to play a dominant role in type II hypersensitivity reactions." *See* Response to first Office Action, page 13, second full paragraph. Furthermore, Applicants also identified specific immune system related disorders disclosed in the specification for which the FcR-V polypeptides would be useful in treating[1].

[1] The specification teaches that the FcR-V polypeptides are useful for the diagnosis or treatment of specific immune system-related disorders, including "immune-complex related inflammatory diseases such as rheumatoid arthritis, systemic lupus erythmatosis, autoimmune hemolytic anemia, thromboctyopenia and IgG- or IgE-mediated inflammation, anaphylaxis, allergy ....." *See, e.g.,* page 60, paragraph 0135.

Applicants provided explicit evidence from the specification in their previous response showing a specific biological role for the FcR-V polypeptides (i.e., regulation of the immune and hematopoietic systems) and correlated this role to a specific group of immune system-related disorders. Thus, the specific, substantial, and credible elements under 35 U.S.C. § 101 were met in that such a correlation between the biological activity and the asserted use in specific disease conditions would be, more likely than not, sufficient to convince one of skill in the art of the usefulness of the FcR-V protein. Therefore, Applicants have provided evidence of a specific, substantial, and credible utility and have clearly met their burden in rebutting the *prima facie* assertion of lack of utility. *See,* M.P.E.P. 2107 (II)(3)(i).

The Examiner also alleged in the first office action response that "there is no information pertaining to the significance of the percentage of homology, e.g. whether there were any conserved motifs that would [have] led the artisan to accept the protein's function." *See*, Paper No. 92004, page 4. In response, Applicants pointed to specific locations in the specification that disclosed and discussed the importance of the conserved domains between FcR-V and the Fc-γ2 receptor, as well as shared conserved domains between the well-established family of FcR receptors. *See,* Response to first Office Action, page 14, first full paragraph. *See also*, specification pages 4 and 5, paragraph 0012; page 19, paragraphs 0038-0039; and Figure 14.

Additionally, Applicants pointed to the reference by Raghavan *et al.*, cited in the specification, which discloses that "receptors for the Fc domain of immunoglobulins play an important role in immune defense" and the "biological responses elicited [by Fc receptors] include antibody-dependent, cell-mediated cytotoxicity, phagocytosis, release of inflammatory mediators, and regulation of lymphocyte proliferation and differentiation. *See Id.* at page 19, paragraph 0039. *See also*, Raghavan *et al.*, abstract (previously submitted as reference AG with the IDS filed August 16, 2004). The Raghavan *et al.* reference provides further support for the asserted utility by providing additional discussion on the importance of the conserved domains of Fc receptors, by discussing the involvement of Fc receptors in immune defense, and by providing evidence that the science related to Fc receptors was well-known at the time of earliest filing of the present application.

Applicants assert that the disclosure of both the conserved Fc receptor domains of the FcR-V polypeptide and the reference by Raghaven *et al.* further support the credibility of the asserted specific, substantial, and well-established utility for the FcR-V polypeptide and the corresponding antibodies of the present invention. More specifically, when presented with the evidence indicating that: 1) Fc receptor involvement in immune defense was well-known; 2) Fc receptors contain hallmark Ig-like conserved domains; and 3) the FcR-V polypeptide of the present application contains all hallmark Ig-like domains of Fc receptors, one of skill in the art would expect that the FcR-V polypeptides, and thus antibodies that bind FcR-V, would be useful in treating and/or diagnosing disorders of the immune system, such as, for example, allergy and inflammation.

Despite the evidence presented by Applicants in response to the first office action and summarized herein above, the Examiner responded by issuing a final utility rejection that is *nearly verbatim* to the utility rejection presented in the first office action. *Compare* Paper No. 92004, page 3, last paragraph to page 5, second full paragraph *and* Paper No. 42005, page 3, first full paragraph to page 5, second full paragraph. Applicants respectfully submit that the response provided by the Examiner is improper. As stated in the M.P.E.P.:

> Office personnel are reminded that they must treat as true a statement of fact made by an applicant in relation to an asserted utility, unless countervailing evidence can be provided that shows that one of ordinary skill in the art would have a legitimate basis to doubt the credibility of such a statement.

Therefore,

> [i]f the applicant responds to the *prima facie* rejection, the Office personnel should review the original disclosure, any evidence relied upon in establishing the prima *facie* showing, any claim amendments, and any new reasoning or evidence provided by the applicant in support of an asserted specific and substantial credible utility. It is essential for Office personnel to recognize, fully consider and respond to each substantive element of any response to a rejection based on lack of utility.

See M.P.E.P. § 2107(II)(D) (emphasis added).

Moreover, the Examiner's response:

> must establish that it is more likely than not that a person of ordinary skill in the art would not consider that any utility asserted by the applicant would be specific and substantial. The prima facie showing must contain the following elements: (i) An explanation that clearly sets forth the reasoning used in concluding that the asserted utility for the claimed invention is not both specific and substantial nor well-established; (ii) Support for factual findings relied upon in reaching this conclusion; and (iii) An evaluation of all relevant evidence of record, including utilities taught in the closest prior art.

See Id. at § 2107(II)(C)(1)(i-iii) (emphasis added).

Given that the presently pending Final Office Action is nearly a verbatim copy of the previous action, it is readily apparent that the Examiner has not responded to "each substantive element" provided in Applicant's rebuttal argument as required by the M.P.E.P.. This is most particularly apparent as it relates to the significance of the conserved domains for FcR-V or the cited Raghaven *et al.* reference, both of which are disclosed in the specification. Most importantly, the Examiner has not provided any explanation, support, or evidence regarding why one of skill in the art would not believe the asserted utility disclosed in the specification when: 1) presented with the knowledge that the FcR-V polypeptide contains all hallmark conserved domains of Fc receptors; 2) given the well-established roles and biological functions of Fc receptors discussed in Raghavan; and 3) provided with information showing that the Fc receptor art was well-known at the time of the earliest filing of the present application.

In addition to the evidence and explanations previously provided, Applicants herein also point out that the specification teaches that FcR-V polypeptides are expressed by activated monocytes, primary dendritic cells, and macrophages. *See, e.g.*, page 13, paragraph 0024. Hence, given the homology of FcR-V to immune system regulatory molecules[2] with the described tissue expression exclusively in cells of the immune system, one of ordinary

[2] FcR-V contains three pairs of the Ig-like domains in its extracellular domain located around the three pairs of cysteine residues located at positions 33 and 81, 139 and 179, and 228 and 279 of SEQ ID NO:10. The Fc-γ2 receptor is thought to be important in modulation of the immune and hematopoietic systems. The homology

skill in the art would immediately appreciate that the presently claimed antibodies would be useful in regulating immune system functions.

To corroborate the asserted utility for the FcR-V polypeptide, Applicants previously submitted the post-filing date publication by Tedla *et al.* Applicants provided a sequence alignment showing that the LIR7 polypeptide sequence and the FcR-V polypeptide were identical at amino acid positions –16 to 449. Furthermore, Applicants pointed out that both the LIR7 and FcR-V amino acid sequences have Ig-like domains characteristic of FcRs in addition to short cytoplasmic domains and positively charged arginine residues within their transmembrane domains that are characteristic of activating LIRs. Finally, Applicants disclosed that LIR7 activates immunological and/or inflammatory responses which are well-known to play important roles in host responses to inflammation, allergic diseases and parasitic infections. From this information, Applicants explained that Tedla *et al.* further corroborates the asserted utility that FcR-V polypeptides, and thus, that one of ordinary skill in the art would expect antibodies that bind FcR-V to be useful in treating and/or diagnosing disorders of the immune system, such as allergy and inflammation.

Nonetheless, the Examiner alleges that "the sequence of LIR-7 has been disclosed by Borges *et al.* not by Tedla *et al.*, and that sequence alignment of the claimed SEQ ID NO:10 does not show 100% identity over the referenced polypeptide." See, Paper No. 42005, page 5 fourth full paragraph. In support of this argument, the Examiner provided the results of a database search from SwissProt_42 database search showing an alignment of 465 amino acids of the FcR-V polypeptide vs. a 482 amino acid sequence.

Applicants respectfully disagree with the Examiner's conclusion. An analysis of the features section of both the SwissProt_42 analysis provided by the Examiner and the NCBI protein sequence database search for Accession No. Q8N149 (submitted herewith as Exhibit A) reveals that the protein sequence provided by the Examiner actually contains a splice variant at amino acid region 419 to 436. Thus, removal of the splice variant yields a 466 amino acid sequence which was identified by Applicants as LIR7 and which is identical to FcR-V at positions –16 to 449 (SEQ ID NO:10).

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between the Fc-γ2 receptor and FcR-V indicates that FcR-V may also be involved in modulation of the immune and hematopoietic systems. *See, e.g.*, pages 19-20, paragraph 0039.

As further evidence that LIR7 is the 466 amino acid sequence previously aligned with FcR-V, Applicants provide herewith the results of a BLAST of the NCBI refseq_human_aa database. The BLAST was performed with the FcR-V polypeptide sequence and the results show 100% alignment over 465 amino acids with the NCBI protein Accession No. NP_006857.1. *See* BLAST results for alignment gi | 5803068 provided herewith as Exhibit B. An NCBI protein sequence database search result for Accession No. NP_006857.1 (submitted herewith as Exhibit C) identifies this 466 amino acid protein as "leukocyte immunogobulin-like receptor 7" (i.e., LIR7) (*See* "Features" section). Furthermore, the search results also list as Reference 2 (residues 1 to 466) the Tedla *et al.* reference referred to by Applicants herein above and in the previous office action response to corroborate the asserted utility for the FcR-V polypeptide. Thus, Applicants maintain their assertion that the Tedla *et al.* reference further corroborates the asserted utility of the present invention.

Furthermore, the Ig-like domains characteristic of the Fc receptors and the short cytoplasmic domains and positively charged arginine residues within the transmembrane domains, which are characteristic of activating LIRs, are identical between FcR-V and LIR7. Given the that these domains were well-known as significant contributors to the FcR protein's biological function and given the well-established involvement of FcR proteins in immune responses, one of skill in the art would more likely than not find the asserted utility of the present invention to be specific, substantial, and credible.

Finally, while the Examiner's concedes that "Tedla et al., further teach that LIR7 may have a possible function in tempering Th2 cell dependent inflammatory response" the Examiner alleges that there "is no recitation of FcR-V polypeptide or possible function of said polypeptide in inflammatory response." *See,* Paper No. 42005, page 5, fourth full paragraph.

Initially, Applicants assert that the FcR-V polypeptides, and thus, antibodies that bind FcR-V, are useful in treating and/or diagnosing disorders of the immune system, such as allergy and inflammation. As pointed out in the response to the first office action, the specification teaches that the FcR-V polypeptides, which are important in the regulation of the immune and hematopoietic systems, are "thought to function as an important trigger of complex immune defense responses including phagocytosis, antibody-dependent cellular

cytotoxicity, and release of inflammatory mediators" and "appear to play a role in an early step in type II hypersensitivity reactions." *See*, specification, page 16, paragraph 0032. Additionally, the specification teaches that the FcR-V polypeptides are useful for the diagnosis and/or treatment of specific immune system-related disorders, including

> immune-complex related inflammatory diseases such as rheumatoid arthritis, systemic lupus erythmatosis, autoimmune hemolytic anemia, thromboctyopenia and IgG- or IgE-mediated inflammation, anaphylaxis, allergy ....."

See, e.g., page 60, paragraph 0135. Therefore, the specification clearly provides sufficient utility for the FcR-V polypeptide in immune system disorders.

In view of the evidence presented in the response to the first office action and summarized herein, Applicants assert that the totality of the record shows that the asserted utility is well-established, specific, substantial, and credible and therefore the rejection under 35 U.S.C. §101 should be withdrawn. Furthermore, the above evidence and explanations clearly show that the claimed invention has at least one or more patentable utilities. Therefore, Applicants respectfully submit that the rejection of claims 23-36, 40-53, 57-66, and 70-79 under 35 U.S.C. §101 has been obviated and respectfully request that the rejection of the claims be reconsidered and withdrawn.

Rejection of claims 23-36, 40-53, 57-66, and 70-79 under 35 U.S.C. § 112, first paragraph

The rejection of claims 23-36, 40-53, 57-66, and 70-79 under 35 U.S.C. § 112, first paragraph, is maintained based on the premise that "since the claimed invention is not supported by either a specific and substantial, asserted utility or a well established utility for the reasons set forth in the rejection under 35 USC § 101 above, one skilled in the art clearly would not know how to use the claimed invention." *See*, Paper No. 42005, page 6, item 8.

Applicants respectfully disagree and traverse.

Applicants respectfully submit that, as explained above, claims 23-36, 40-53, 57-66, and 70-79 are supported by specific, substantial, and/or well-established utilities. Hence, in view of the present application's disclosure and the state of the art as of its earliest filing date, Applicants submit that a person having ordinary skill in the art would certainly know how to use the claimed invention. Accordingly, Applicants respectfully request the rejection of

pending claims 23-36, 40-53, 57-66, and 70-79 under 35 U.S.C. § 112, first paragraph, be reconsidered and withdrawn.

Rejection of Claims 57-66 and 70-79 under 35 U.S.C. § 112, first paragraph

The rejection of claims 57-66 and 70-79 under 35 U.S.C. § 112, first paragraph, is maintained for allegedly "containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." *See*, Paper No. 42005, page 6-7, item 9. In particular, it is asserted that:

> Applicant mistakenly assumes that the disclosure of "cell expressing FcR-V" is an equivalent of "FcR-V protein expressed on the surface of a cell". The genus of "Cells expressing FcR-V" reads on soluble FcR-V and membrane-bound FcR-V, while subgenus "FcR-V protein expressed on the suface of a cell" reads only on a membrane-bound form of FcR-V.

See Id. at page 7, item 12, third full paragraph.

In response, Applicants have herein amended independent claims 57 and 70 to read "An isolated antibody or fragment thereof that specifically binds a FcR-V protein expressed from a cell...". Support for this amendment can be found, for example, at page 2, paragraph 0006; and, pages 8-11, paragraph 0017. Accordingly, the rejection to claims 57-66 and 70-79 has been obviated. Thus, Applicants respectfully request that the Examiner's rejection of claims 57-66 and 70-79 under 35 U.S.C. § 112, first paragraph be reconsidered and withdrawn.

Conclusion

Applicants respectfully request that the above-made amendments and remarks be entered and made of record in the file history of the instant application. The Examiner is invited to call the undersigned at the phone number provided below if any further action by Applicant would expedite the examination of this application. If there are any fees due in connection with the filing of this paper, please charge the fees to our Deposit Account No. 08-3425.

Date: 7/21/2005

Respectfully submitted,

Doyle A. Siever (Reg. No. 47,088)
Agent for Applicants

Human Genome Sciences, Inc.
14200 Shady Grove Road
Rockville, Maryland 20850
(301) 354-3932 (Phone)

MJP/DAS/PF/ba


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LOCUS       Q8N149                  483 aa            linear   PRI 01-MAY-2005
DEFINITION  Leukocyte immunoglobulin-like receptor subfamily A member 2
            precursor (Leucocyte immunoglobulin like receptor 7) (LIR-7)
            (Immunoglobulin-like transcript 1) (ILT-1) (CD85h antigen).
ACCESSION   Q8N149
VERSION     Q8N149  GI:37537906
DBSOURCE    swissprot: locus LIRA2_HUMAN, accession Q8N149;
            class: standard.
            extra accessions:O75020,created: Oct 10, 2003.
            sequence updated: Oct 10, 2003.
            annotation updated: May 1, 2005.
            xrefs: AF025531.1, AAB87665.1, BC017412.1, AAH17412.1, BC027916.1,
            AAH27916.1
            xrefs (non-sequence databases): HSSPQ8NHL6, EnsemblENSG00000187095,
            GenewHGNC:6603, MIM 604812, GO0003823, GO0004872, GO0006952,
            GO0007165, InterProIPR003599, InterProIPR007110, PfamPF00047,
            SMARTSM00409, PROSITEPS50835
KEYWORDS    Alternative splicing; Antigen; Glycoprotein; Immune response;
            Immunoglobulin domain; Multigene family; Polymorphism; Receptor;
            Repeat; Signal; Transmembrane.
SOURCE      Homo sapiens (human)
  ORGANISM  Homo sapiens
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Euarchontoglires; Primates; Catarrhini;
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REFERENCE   1  (residues 1 to 483)
  AUTHORS   Borges,L., Hsu,M.L., Fanger,N., Kubin,M. and Cosman,D.
  TITLE     A family of human lymphoid and myeloid Ig-like receptors, some of
            which bind to MHC class I molecules
  JOURNAL   J. Immunol. 159 (11), 5192-5196 (1997)
   PUBMED   9548455
  REMARK    NUCLEOTIDE SEQUENCE (ISOFORM 1), AND TISSUE SPECIFICITY.
            TISSUE=Peripheral blood leukocytes
REFERENCE   2  (residues 1 to 483)
  AUTHORS   Strausberg,R.L., Feingold,E.A., Grouse,L.H., Derge,J.G.,
            Klausner,R.D., Collins,F.S., Wagner,L., Shenmen,C.M., Schuler,G.D.,
            Altschul,S.F., Zeeberg,B., Buetow,K.H., Schaefer,C.F., Bhat,N.K.,
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            Stapleton,M., Soares,M.B., Bonaldo,M.F., Casavant,T.L.,
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            McKernan,K.J., Malek,J.A., Gunaratne,P.H., Richards,S.,
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            Sanchez,A., Whiting,M., Madan,A., Young,A.C., Shevchenko,Y.,
            Bouffard,G.G., Blakesley,R.W., Touchman,J.W., Green,E.D.,
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            Butterfield,Y.S., Krzywinski,M.I., Skalska,U., Smailus,D.E.,
            Schnerch,A., Schein,J.E., Jones,S.J. and Marra,M.A.
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  JOURNAL   Proc. Natl. Acad. Sci. U.S.A. 99 (26), 16899-16903 (2002)
   PUBMED   12477932
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COMMENT      [FUNCTION] May act as receptor for class I MHC antigens.
             [SUBCELLULAR LOCATION] Type I membrane protein.
             [ALTERNATIVE PRODUCTS] Event=Alternative splicing; Named
             isoforms=2; Name=1; IsoId=Q8N149-1; Sequence=Displayed; Name=2;
             IsoId=Q8N149-2; Sequence=VSP_008455; Note=No experimental
             confirmation available.
             [TISSUE SPECIFICITY] Expression levels are very low or not
             detectable on monocytes, T-cells, B-cells, dendritic cells and
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             [SIMILARITY] Contains 4 immunoglobulin-like C2-type domains.
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      481 agr
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//

Feb 9 2005 14:31:10

BLAST Results for Result 4416111

BLAST results for sequence
PF363-FcRV

Accession numbers are hotlinked to Entrez at NCBI
The description is hotlinked to the alignment, further down the page

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BLASTP 2.0MP-WashU [15-Jun-2000] [sol7-ultra-L64 12:00:28 20-Jun-2000]

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Reference:  Gish, W. (1996-2000) http://blast.wustl.edu

Query=  PF363-FcRV
        (514 letters)

Database:  /usr/ncbi/blast/db/refseq_human_aa
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Searching....10....20....30....40....50....60....70....80....90....100% done
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Sequences producing High-scoring Segment Pairs:			High Score	Smallest Sum Probability P(N)	N
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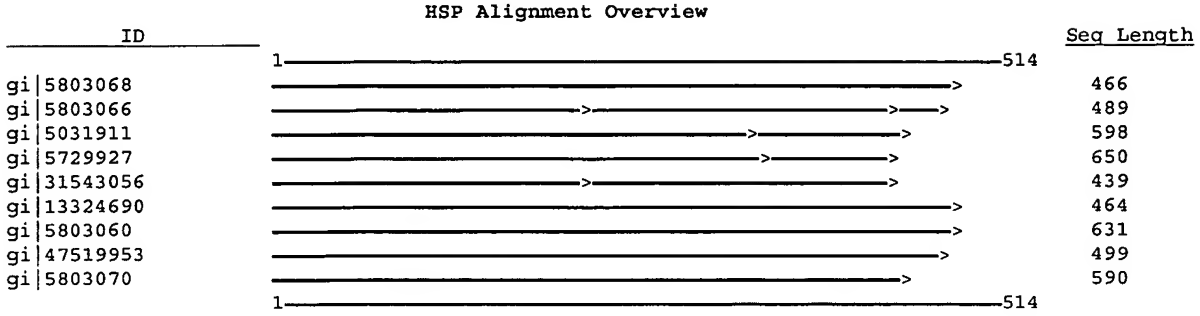
gi|5803066	ref|NP_006854.1|	leukocyte immunoglobulin-lik...	1734	1.2e-196	2
gi|5031911	ref|NP_005865.1|	leukocyte immunoglobulin-lik...	1749	1.6e-183	2
gi|5729927	ref|NP_006660.1|	leukocyte immunoglobulin-lik...	1759	2.2e-182	1
gi|31543056	ref|NP_006856.2|	leukocyte immunoglobulin-lik...	1756	4.7e-182	1
gi|13324690	ref|NP_077294.1|	leukocyte immunoglobulin-lik...	1687	9.6e-175	1
gi|5803060	ref|NP_006855.1|	leukocyte immunoglobulin-lik...	1493	3.5e-154	1
gi|47519953	ref|NP_036408.3|	leukocyte immunoglobulin-lik...	1474	3.6e-152	1
gi|5803070	ref|NP_006831.1|	leukocyte immunoglobulin-lik...	1330	3.0e-139	2
gi|13399320	ref|NP_077293.1|	leukocyte immunoglobulin-lik...	884	3.1e-101	2
gi|32895361	ref|NP_870994.1|	leukocyte Ig-like receptor 9...	637	1.8e-63	1
gi|32490553	ref|NP_067073.1|	leukocyte Ig-like receptor 9...	636	2.3e-63	1
gi|46488946	ref|NP_703144.2|	killer cell immunoglobulin-l...	579	2.5e-57	1
gi|5803052	ref|NP_006728.1|	killer cell immunoglobulin-l...	555	8.7e-55	1
gi|32895365	ref|NP_871715.1|	leukocyte Ig-like receptor 9...	544	1.3e-53	1
gi|21314641	ref|NP_006838.2|	leukocyte immunoglobulin-lik...	543	1.6e-53	1
gi|32895363	ref|NP_871714.1|	leukocyte Ig-like receptor 9...	543	1.6e-53	1
gi|7019441	ref|NP_037421.1|	killer cell immunoglobulin-l...	538	5.5e-53	1
gi|45505167	ref|NP_001546.2|	immunoglobulin superfamily, ...	545	1.8e-52	1
gi|37574620	ref|NP_057447.3|	glycoprotein VI (platelet); ...	437	2.8e-42	1
gi|41208929	ref|XP_372748.1|	similar to 1060P11.3 (killer...	433	7.3e-42	1
gi|41151816	ref|XP_373336.1|	similar to 1060P11.3 (killer...	430	1.5e-41	1
gi|7705568	ref|NP_056952.1|	killer cell immunoglobulin-l...	423	8.4e-41	1
gi|6912472	ref|NP_036444.1|	killer cell immunoglobulin-l...	417	3.6e-40	1
gi|7657273	ref|NP_055034.1|	killer cell immunoglobulin-l...	409	2.6e-39	1
gi|7657271	ref|NP_055033.1|	killer cell immunoglobulin-l...	401	1.8e-38	1
gi|4758692	ref|NP_004820.1|	natural cytotoxicity trigger...	340	2.0e-37	2
gi|7657277	ref|NP_055327.1|	killer cell immunoglobulin-l...	385	8.9e-37	1
gi|11968154	ref|NP_065396.1|	killer cell immunoglobulin-l...	382	1.9e-36	1
gi|7657279	ref|NP_055328.1|	killer cell immunoglobulin-l...	369	3.8e-36	2
gi|6912474	ref|NP_036445.1|	killer cell immunoglobulin-l...	375	1.0e-35	1
gi|31982878	ref|NP_002246.3|	killer cell immunoglobulin-l...	363	1.9e-34	1
gi|19743857	ref|NP_579803.1|	Fc alpha receptor isoform b ...	274	3.2e-33	2
gi|19743871	ref|NP_579813.1|	Fc alpha receptor isoform i ...	345	2.1e-32	1
gi|4503673	ref|NP_001991.1|	Fc alpha receptor isoform a ...	342	4.8e-32	1
gi|45580713	ref|NP_570127.2|	osteoclast-associated recept...	331	9.2e-31	1
gi|19557664	ref|NP_573398.1|	osteoclast-associated recept...	330	1.2e-30	1
gi|19557668	ref|NP_573399.1|	osteoclast-associated recept...	329	1.6e-30	1
gi|19743861	ref|NP_579806.1|	Fc alpha receptor isoform d;...	310	2.2e-28	1
gi|19743869	ref|NP_579812.1|	Fc alpha receptor isoform h;...	227	5.5e-28	2
gi|19743873	ref|NP_579814.1|	Fc alpha receptor isoform j;...	298	4.9e-27	1
gi|46397359	ref|NP_036446.2|	killer cell immunoglobulin-l...	286	1.0e-25	1
gi|46397357	ref|NP_839942.2|	killer cell immunoglobulin-l...	286	1.0e-25	1
gi|45580719	ref|NP_996554.1|	osteoclast-associated recept...	271	4.7e-24	1
gi|19743867	ref|NP_579811.1|	Fc alpha receptor isoform g;...	264	2.8e-23	1

gi|45580717 ref|NP_996553.1| osteoclast-associated recept...	234	5.3e-20	1
gi|21071030 ref|NP_570602.2| alpha 1B-glycoprotein [Homo ...	241	1.5e-18	1
gi|33589850 ref|NP_055326.2| killer cell immunoglobulin-l...	214	7.9e-18	1
gi|19743865 ref|NP_579808.1| Fc alpha receptor isoform f;...	211	1.7e-17	1
gi|10947103 ref|NP_067154.1| leukocyte-associated Ig-like...	209	2.8e-17	1

HSP Alignment Overview



WARNING: Descriptions of 92 database sequences were not reported due to the limiting value of parameter V = 50.

>gi|5803068 ref|NP_006857.1| leukocyte immunoglobulin-like receptor, subfamily A (with TM domain), member 2; leukocyte immunoglobulin-like receptor 7 [Homo sapiens]
Length = 466

Score = 2489 (881.2 bits), Expect = 9.9e-260, P = 9.9e-260
Identities = 465/465 (100%), Positives = 465/465 (100%)

```
Query:     1 MTPILTVLICLGLSLGPRTHVQAGHLPKPTLWAEPGSVIIQGSPVTLRCQGSLQAEEYHL 60
             MTPILTVLICLGLSLGPRTHVQAGHLPKPTLWAEPGSVIIQGSPVTLRCQGSLQAEEYHL
Sbjct:     1 MTPILTVLICLGLSLGPRTHVQAGHLPKPTLWAEPGSVIIQGSPVTLRCQGSLQAEEYHL 60

Query:    61 YRENKSASWVRRIQEPGKNGQFPIPSITWEHAGRYHCQYYSHNHSSEYSDPLELVVTGAY 120
             YRENKSASWVRRIQEPGKNGQFPIPSITWEHAGRYHCQYYSHNHSSEYSDPLELVVTGAY
Sbjct:    61 YRENKSASWVRRIQEPGKNGQFPIPSITWEHAGRYHCQYYSHNHSSEYSDPLELVVTGAY 120

Query:   121 SKPTLSALPSPVVTLGGNVTLQCVSQVAFDGFILCKEGEDEHPQRLNSHSHARGWSWAIF 180
             SKPTLSALPSPVVTLGGNVTLQCVSQVAFDGFILCKEGEDEHPQRLNSHSHARGWSWAIF
Sbjct:   121 SKPTLSALPSPVVTLGGNVTLQCVSQVAFDGFILCKEGEDEHPQRLNSHSHARGWSWAIF 180

Query:   181 SVGPVSPSRRWSYRCYAYDSNSPYVWSLPSDLLELLVPGVSKKPSLSVQPGPMVAPGESL 240
             SVGPVSPSRRWSYRCYAYDSNSPYVWSLPSDLLELLVPGVSKKPSLSVQPGPMVAPGESL
Sbjct:   181 SVGPVSPSRRWSYRCYAYDSNSPYVWSLPSDLLELLVPGVSKKPSLSVQPGPMVAPGESL 240

Query:   241 TLQCVSDVGYDRFVLYKEGERDFLQRPGWQPQAGLSQANFTLGPVSPSHGGQYRCYSAHN 300
             TLQCVSDVGYDRFVLYKEGERDFLQRPGWQPQAGLSQANFTLGPVSPSHGGQYRCYSAHN
Sbjct:   241 TLQCVSDVGYDRFVLYKEGERDFLQRPGWQPQAGLSQANFTLGPVSPSHGGQYRCYSAHN 300

Query:   301 LSSEWSAPSDPLDILITGQFYDRPSLSVQPVPTVAPGKNVTLLCQSRGQFHTFLLTKEGA 360
             LSSEWSAPSDPLDILITGQFYDRPSLSVQPVPTVAPGKNVTLLCQSRGQFHTFLLTKEGA
Sbjct:   301 LSSEWSAPSDPLDILITGQFYDRPSLSVQPVPTVAPGKNVTLLCQSRGQFHTFLLTKEGA 360

Query:   361 GHPPLHLRSEHQAQQNQAEFRMGPVTSAHVGTYRCYSSLSSNPYLLSLPSDPLELVVSAS 420
             GHPPLHLRSEHQAQQNQAEFRMGPVTSAHVGTYRCYSSLSSNPYLLSLPSDPLELVVSAS
Sbjct:   361 GHPPLHLRSEHQAQQNQAEFRMGPVTSAHVGTYRCYSSLSSNPYLLSLPSDPLELVVSAS 420

Query:   421 LGQHPQDYTVENLIRMGVAGLVLVVLGILLFEAQHSQRSLQDAAG 465
             LGQHPQDYTVENLIRMGVAGLVLVVLGILLFEAQHSQRSLQDAAG
Sbjct:   421 LGQHPQDYTVENLIRMGVAGLVLVVLGILLFEAQHSQRSLQDAAG 465
```

>gi|5803066 ref|NP_006854.1| leukocyte immunoglobulin-like receptor, subfamily A (with TM domain), member 1; leukocyte immunoglobulin-like receptor 6 [Homo sapiens]
Length = 489

Score = 1734 (615.5 bits), Expect = 1.2e-196, Sum P(2) = 1.2e-196
Identities = 340/422 (80%), Positives = 355/422 (84%)

```
Query:     1 MTPILTVLICLGLSLGPRTHVQAGHLPKPTLWAEPGSVIIQGSPVTLRCQGSLQAEEYHL 60
             MTPI+TVLICL LSLGPRTHVQAG LPKPTLWAEPGSVI QGSPVTL CQG L+ +EY L
Sbjct:     1 MTPIVTVLICLRLSLGPRTHVQAGTLPKPTLWAEPGSVITQGSPVTLWCQGILETQEYRL 60

Query:    61 YRENKSASWVRRI-QEPGKNGQFPIPSITWEHAGRYHCQYYSHNHS-SEYSDPLELVVTG 118
             YRE K+A W+ RI QE  K GQFPIPSITWEH GRY C Y SH    SE SDPLELVVTG
Sbjct:    61 YREKKTAPWITRIPQEIVKKGQFPIPSITWEHTGRYRCFYGSHTAGWSEPSDPLELVVTG 120

Query:   119 AYSKPTLSALPSPVVTLGGNVTLQCVSQVAFDGFILCKEGEDEHPQRLNSHSHARGWSWA 178
             AY KPTLSALPSPVVT GGNVTL CVSQVAF  FILCKEGEDEHPQ LNS     GWS A
Sbjct:   121 AYIKPTLSALPSPVVTSGGNVTLHCVSQVAFGSFILCKEGEDEHPQCLNSQPRTHGWSRA 180

Query:   179 IFSVGPVSPSRRWSYRCYAYDSNSPYVWSLPSDLLELLVPGVSKKPSLSVQPGPMVAPGE 238
             IFSVGPVSPSRRWSYRCYAYDSNSP+VWSLPSDLLELLV GVSKKPSLSVQPGP+VAPGE
Sbjct:   181 IFSVGPVSPSRRWSYRCYAYDSNSPHVWSLPSDLLELLVLGVSKKPSLSVQPGPIVAPGE 240

Query:   239 SLTLQCVSDVGYDRFVLYKEGERDFLQRPGWQPQAGLSQANFTLGPVSPSHGGQYRCYSA 298
             SLTLQCVSDV YDRFVLYKEGERDFLQ PG QPQAGLSQANFTLGPVS S+GGQYRC  A
Sbjct:   241 SLTLQCVSDVSYDRFVLYKEGERDFLQLPGPQPQAGLSQANFTLGPVSRSYGGQYRCSGA 300

Query:   299 HNLSSEWSAPSDPLDILITGQFYDRPSLSVQPVPTVAPGKNVTLLCQSRGQPHTFLLTKE 358
             +NLSSEWSAPSDPLDILI GQF  RP +SV P PTVA G+NVTLLCQS G FHTFLLTK
Sbjct:   301 YNLSSEWSAPSDPLDILIAGQFRGRPFISVHPGPTVASGENVTLLCQSWGPFHTFLLTKA 360

Query:   359 GAGHPPLHLRSEHQAQQNQAEFRMGPVTSAHVGTYRCYSSLSSNPYLLSLPSDPLELVVS 418
             GA   PL LRS H+  + QAEF M PVTSAH GTYRCY SLSSNPYLLS PSD LEL+VS
Sbjct:   361 GAADAPLRLRSIHEYPKYQAEFPMSPVTSAHSGTYRCYGSLSSNPYLLSHPSDSLELMVS 420

Query:   419 AS 420
              +
Sbjct:   421 GA 422

 Score = 477 (173.0 bits), Expect = 6.7e-64, Sum P(2) = 6.7e-64
 Identities = 126/321 (39%), Positives = 177/321 (55%)

Query:   111 PLELVVTGAYSKPTLSALPSPVVTLGGNVTLQCVSQVAFDGFILCKEGEDEHP--QRLNS 168
             P   V  G   KPTL A P  V+T G  VTL C   +    + L +E +   P   R+
Sbjct:    17 PRTHVQAGTLPKPTLWAEPGSVITQGSPVTLWCQGILETQEYRLYREKKTA-PWITRIPQ 75

Query:   169 HSHARGWSWAIFSVGPVSPSRRWSYRCYAYDSNSPYVWSLPSDLLELLVPGVSKKPSLSV 228
                 +G     F +  ++       YRC+ Y S++   WS PSD LEL+V G   KP+LS
Sbjct:    76 EIVKKGQ----FPIPSITWEHTGRYRCF-YGSHTAG-WSEPSDPLELVVTGAYIKPTLSA 129

Query:   229 QPGPMVAPGESLTLQCVSDVGYDRFVLYKEGERDFLQRPGWQPQA-GLSQANFTLGPVSP 287
              P P+V  G ++TL CVS V +  F+L KEGE +  Q    QP+  G S+A F++GPVSP
Sbjct:   130 LPSPVVTSGGNVTLHCVSQVAFGSFILCKEGEDEHPQCLNSQPRTHGWSRAIFSVGPVSP 189

Query:   288 SHGGQYRCYSAHNLSSE-WSAPSDPLDILITGQFYDRPSLSVQPVPTVAPGKNVTLLCQS 346
             S    YRCY+  + S   WS PSD L++L+ G    +PSLSVQP P VAPG+++TL C S
Sbjct:   190 SRRWSYRCYAYDSNSPHVWSLPSDLLELLVLG-VSKKPSLSVQPGPIVAPGESLTLQCVS 248

Query:   347 RGQFHTFLLTKEGAGHPPLHLRS-EHQAQQNQAEFRMGPVTSAHVGTYRCYSSLS-SNPY 404
                +  F+L KEG     L L   + QA  +QA F +GPV+ ++ G YRC  + + S+ +
Sbjct:   249 DVSYDRFVLYKEGE-RDFLQLPGPQPQAGLSQANFTLGPVSRSYGGQYRCSGAYNLSSEW 307

Query:   405 LLSLPSDPLELVVSASLGQHP 425
               S PSDPL+++++      P
Sbjct:   308 --SAPSDPLDILIAGQFRGRP 326

 Score = 285 (105.4 bits), Expect = 1.4e-38, Sum P(2) = 1.4e-38
 Identities = 71/207 (34%), Positives = 112/207 (54%)

Query:    28 KPTLWAEPGSVIIQGSPVTLRCQGSLQAEEYHLYRENKSASWVRRIQEPGKNGQ------ 81
             KP+L  +PG ++  G  +TL+C   +  + + LY+E +          +Q PG   Q
Sbjct:   225 KPSLSVQPGPIVAPGESLTLQCVSDVSYDRFVLYKEGERDF----LQLPGPQPQAGLSQA 280

Query:    82 -FPIPSITWEHAGRYHCQYYSHNHSSEYS---DPLELVVTGAY-SKPTLSALPSPVVTLG 136
              F +  ++  + G+Y C    ++N SSE+S   DPL++++ G +  +P +S   P P V  G
Sbjct:   281 NFTLGPVSRSYGGQYRCSG-AYNLSSEWSAPSDPLDILIAGQFRGRPFISVHPGPTVASG 339

Query:   137 GNVTLQCVSQVAFDGFILCKEGEDEHPQRLNS-HSHARGWSWAIFSVGPVSPSRRWSYRC 195
              NVTL C S   F  F+L K G  + P RL S H + +    A F + PV+ +   +YRC
Sbjct:   340 ENVTLLCQSWGPFHTFLLTKAGAADAPLRLRSIHEYPK--YQAEFPMSPVTSAHSGTYRC 397

Query:   196 YAYDSNSPYVWSLPSDLLELLVPGVSK 222
```

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            Y   S++PY+ S PSD LEL+V G ++
Sbjct:   398 YGSLSSNPYLLSHPSDSLELMVSGAAE 424

 Score = 182 (69.1 bits), Expect = 1.2e-196, Sum P(2) = 1.2e-196
 Identities = 36/37 (97%), Positives = 37/37 (100%)

Query:   424 HPQDYTVENLIRMGVAGLVLVVLGILLFEAQHSQRSL 460
            HPQDYTVENLIRMG+AGLVLVVLGILLFEAQHSQRSL
Sbjct:   453 HPQDYTVENLIRMGIAGLVLVVLGILLFEAQHSQRSL 489


>gi|5031911 ref|NP_005865.1| leukocyte immunoglobulin-like receptor, subfamily
            B (with TM and ITIM domains), member 2; leukocyte
            immunoglobulin-like receptor 2 [Homo sapiens]
            Length = 598

 Score = 1749 (620.7 bits), Expect = 1.6e-183, Sum P(2) = 1.6e-183
 Identities = 340/427 (79%), Positives = 361/427 (84%)

Query:     1 MTPILTVLICLGLSLGPRTHVQAGHLPKPTLWAEPGSVIIQGSPVTLRCQGSLQAEEYHL 60
            MTPI+TVLICLGLSLGPRTHVQ G +PKPTLWAEP SVI QGSPVTL COGSL+A+EY L
Sbjct:     1 MTPIVTVLICLGLSLGPRTHVQTGTIPKPTLWAEPDSVITQGSPVTLSCQGSLEAQEYRL 60

Query:    61 YRENKSASWVRRIQ-EPGKNGQFPIPSITWEHAGRYHCQYYSHNHSSEYSDPLELVVTGA 119
            YRE KSASW+ RI+ E  KNGQF IPSITWEH GRY CQYYS    SE SDPL LV+TGA
Sbjct:    61 YREKKSASWITRIRPELVKNGQFHIPSITWEHTGRYGCQYYSRARWSELSDPLVLVMTGA 120

Query:   120 YSKPTLSALPSPVVTLGGNVTLQCVSQVAFDGFILCKEGEDEHPQRLNSHSHARGWSWAI 179
            Y KPTLSA PSPVVT GG VTLQC SQVAF GFILCKEGEDEHPQ LNS  HARG S AI
Sbjct:   121 YPKPTLSAQPSPVVTSGGRVTLQCESQVAFGGFILCKEGEDEHPQCLNSQPHARGSSRAI 180

Query:   180 FSVGPVSPSRRWSYRCYAYDSNSPYVWSLPSDLLELLVPGVSKKPSLSVQPGPMVAPGES 239
            FSVGPVSP+RRWS+RCY YD NSPYVWS PSDLLELLVPGVSKKPSLSVQPGP+VAPGES
Sbjct:   181 FSVGPVSPNRRWSHRCYGYDLNSPYVWSSPSDLLELLVPGVSKKPSLSVQPGPVVAPGES 240

Query:   240 LTLQCVSDVGYDRFVLYKEGERDFLQRPGWQPQAGLSQANFTLGPVSPSHGGQYRCYSAH 299
            LTLQCVSDVGYDRFVLYKEGERD  Q PG QPQAGLSQANFTLGPVS S+GGQYRCY A+
Sbjct:   241 LTLQCVSDVGYDRFVLYKEGERDLRQLPGRQPQAGLSQANFTLGPVSRSYGGQYRCYGAY 300

Query:   300 NLSSEWSAPSDPLDILITGQFYDRPSLSVQPVPTVAPGKNVTLLCQSRGQFHTFLLTKEG 359
            NLSSEWSAPSDPLDILITGQ +  P +SVQP PTVA G+NVTLLCQS  QFHTFLLTK G
Sbjct:   301 NLSSEWSAPSDPLDILITGQIHGTPFISVQPGPTVASGENVTLLCQSWRQFHTFLLTKAG 360

Query:   360 AGHPPLHLRSEHQAQQNQAEFRMGPVTSAHVGTYRCYSSLSSNPYLLSLPSDPLELVVSA 419
            A   PL LRS H+  + QAEF M PVTSAH GTYRCY SL+S+PYLLS PS+PLELVVS
Sbjct:   361 AADAPLRLRSIHEYPKYQAEFPMSPVTSAHAGTYRCYGSLNSDPYLLSHPSEPLELVVSG 420

Query:   420 -SLGQHP 425
             S+G  P
Sbjct:   421 PSMGSSP 427

 Score = 479 (173.7 bits), Expect = 1.7e-49, Sum P(2) = 1.7e-49
 Identities = 125/328 (38%), Positives = 172/328 (52%)

Query:    17 PRTHVQAGHLPKPTLWAEPGSVIIQGSPVTLRCQGSLQAEEYHLYRENKSASWVRRIQEP 76
            P   V  G  PKPTL A+P  V+  G  VTL+C+  +    + L +E +          +P
Sbjct:   112 PLVLVMTGAYPKPTLSAQPSPVVTSGGRVTLQCESQVAFGGFILCKEGEDEHPQCLNSQP 171

Query:    77 GKNGQ----FPIPSITWEHAGRYHCQYYSHNHSSEYSDP---LELVVTGAYSKPTLSALP 129
               G     F +  ++       + C  Y  N    +S P   LEL+V G    KP+LS  P
Sbjct:   172 HARGSSRAIFSVGPVSPNRRWSHRCYGYDLNSPYVWSSPSDLLELLVPGVSKKPSLSVQP 231

Query:   130 SPVVTLGGNVTLQCVSQVAFDGFILCKEGEDEHPQRLNSHSHARGWSWAIFSVGPVSPSR 189
             PVV  G ++TLQCVS V +D F+L KEGE +  Q L       G S A F++GPVS S
Sbjct:   232 GPVVAPGESLTLQCVSDVGYDRFVLYKEGERDLRQ-LPGRQPQAGLSQANFTLGPVSRSY 290

Query:   190 RWSYRCY-AYDSNSPYVWSLPSDLLELLVPG-VSKKPSLSVQPGPMVAPGESLTLQCVSD 247
               YRCY AY+ +S   WS PSD L++L+ G +    P +SVQPGP VA GE++TL C S
Sbjct:   291 GGQYRCYGAYNLSSE--WSAPSDPLDILITGQIHGTPFISVQPGPTVASGENVTLLCQSW 348

Query:   248 VGYDRFVLYKEGERDFLQRPGWQPQAGLSQANFTLGPVSPSHGGQYRCYSAHNLSSEW-- 305
              +  F+L K G  D   R     +    QA F + PV+ +H G YRCY + N S  +
Sbjct:   349 RQFHTFLLTKAGAADAPLRLRSIHEYPKYQAEFPMSPVTSAHAGTYRCYGSLN-SDPYLL 407

Query:   306 SAPSDPLDILITGQFYDRPSLSVQPVPT 333
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LOCUS NP_006857 466 aa linear PRI 22-APR-2005
DEFINITION leukocyte immunoglobulin-like receptor, subfamily A (with TM domain), member 2 [Homo sapiens].
ACCESSION NP_006857
VERSION NP_006857.1 GI:5803068
DBSOURCE REFSEQ: accession NM_006866.1
KEYWORDS .
SOURCE Homo sapiens (human)
ORGANISM Homo sapiens
Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Primates; Catarrhini; Hominidae; Homo.
REFERENCE 1 (residues 1 to 466)
AUTHORS Sloane,D.E., Tedla,N., Awoniyi,M., Macglashan,D.W. Jr., Borges,L., Austen,K.F. and Arm,J.P.
TITLE Leukocyte immunoglobulin-like receptors: novel innate receptors for human basophil activation and inhibition
JOURNAL Blood 104 (9), 2832-2839 (2004)
PUBMED 15242876
REMARK GeneRIF: Cross-linking of basophil LIR7 resulted in the concentration-dependent net release of histamine and cysteinyl leukotrienes that were maximal at 30 minutes, and of IL-4 that was maximal at 4 hours
REFERENCE 2 (residues 1 to 466)
AUTHORS Tedla,N., Bandeira-Melo,C., Tassinari,P., Sloane,D.E., Samplaski,M., Cosman,D., Borges,L., Weller,P.F. and Arm,J.P.
TITLE Activation of human eosinophils through leukocyte immunoglobulin-like receptor 7
JOURNAL Proc. Natl. Acad. Sci. U.S.A. 100 (3), 1174-1179 (2003)
PUBMED 12529506
REMARK GeneRIF: LIR7 is an activating receptor for eosinophils that elicited the release of cytotoxic granule proteins, de novo lipid mediator generation, and cytokine release through vesicular transport
REFERENCE 3 (residues 1 to 466)
AUTHORS Borges,L., Hsu,M.L., Fanger,N., Kubin,M. and Cosman,D.
TITLE A family of human lymphoid and myeloid Ig-like receptors, some of which bind to MHC class I molecules
JOURNAL J. Immunol. 159 (11), 5192-5196 (1997)
PUBMED 9548455
REFERENCE 4 (residues 1 to 466)
AUTHORS Samaridis,J. and Colonna,M.
TITLE Cloning of novel immunoglobulin superfamily receptors expressed on human myeloid and lymphoid cells: structural evidence for new stimulatory and inhibitory pathways
JOURNAL Eur. J. Immunol. 27 (3), 660-665 (1997)
PUBMED 9079806
REFERENCE 5 (residues 1 to 466)
AUTHORS Rojo,S., Burshtyn,D.N., Long,E.O. and Wagtmann,N.
TITLE Type I transmembrane receptor with inhibitory function in mouse mast cells and NK cells
JOURNAL J. Immunol. 158 (1), 9-12 (1997)
PUBMED 8977169
COMMENT PROVISIONAL REFSEQ: This record has not yet been subject to final NCBI review. The reference sequence was derived from U82275.1.

Summary: Leukocyte Ig-like receptors (LIRs) are a family of

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            immunoreceptors expressed predominantly on monocytes and B cells
            and at lower levels on dendritic cells and natural killer (NK)
            cells. All LIRs in subfamily B have an inhibitory function (see,
            e.g., LILRB1, MIM 604811). LIRs in subfamily A, with short
            cytoplasmic domains lacking an immunoreceptor tyrosine-based
            inhibitory motif (ITIM) and with transmembrane regions containing a
            charged arginine residue, may initiate stimulatory cascades. One
            member of subfamily A (LILRA3; MIM 604818) lacks a transmembrane
            region and is presumed to be a soluble receptor.[supplied by OMIM].
FEATURES             Location/Qualifiers
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                     /db_xref="taxon:9606"
                     /chromosome="19"
                     /map="19q13.4"
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                     subfamily A (with TM domain), member 2"
                     /note="leukocyte immunoglobulin-like receptor 7"
     CDS             1..466
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                     /coded_by="NM_006866.1:88..1488"
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                     go_function: antigen binding [goid 0003823] [evidence TAS]
                     [pmid 9548455];
                     go_function: receptor activity [goid 0004872] [evidence
                     TAS] [pmid 9548455];
                     go_process: immune response [goid 0006955] [evidence IEA];
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